antibody production. The important role of transplacental transfer of fetal red blood cells is illustrated in those instances in which the firstborn infant is affected. In the vast majority of these cases, the Rh— mother had previously been transfused and the appearance of antibodies in the latter third of the pregnancy can be interpreted only as the response to antigenic material received in the course of the pregnancy. These cases serve as examples of the specific anamnestic reaction since antibodies resulting from the transfusion of perhaps 10-15 years previously have since disappeared, but they reappear more rapidly in response to the same antigenic stimulus many years later.

Additional evidence to indicate that there is no need to assume gross pathologic lesions in the placenta will be found in the recent papers of Naeslund and Aren, Kline and Everett and Henderson.* It would indeed be remarkable if nature provided an absolutely perfect organ which, like a malignant cell, is endowed with such invasive properties and rapid proliferation that in the short space of 40 weeks it attains a surface area of 70-120 square feet essential for the nourishment of the fetus.

Undoubtedly, further studies will reveal many examples of isoimmunization by fetal blood in other species of animals, especially those characterized by a type of placenta which does not differ much from that in man. Curiously enough, the first successful demonstration was in horses in which there are four layers of tissue cells separating the two circulations. Because maternal antibodies of the mare do not pass into the fetus, the disease does not occur in utero but only after ingestion of colostrum which is so rich in antibodies.[12, 13]

* For references see Levine.[11(b)]

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Recent Views on the Genetics of the Rh-Hr Blood Factors

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At least 6 Rh-Hr antigens are known to exist. Credit for their discovery must be given to Landsteiner and Wiener, Levine, Race, Mourant, and Diamond. Originally the 6 antigens were called Rh′, Hr′, Rh_0, Hr_0, Rh″ and Hr″. In 1944 the British investigators, Fisher and Race, introduced another set of names known as the CDE system. Because of its simplicity and descriptiveness this system is gaining favor with many investigators, not only in Europe but in the Americas as well. It is the system which I personally prefer, primarily because I teach large classes in human

genetics and find that it is much more readily accepted by students. I should, however, like to see the symbol Rh shown before the CDE letters whenever it might not otherwise be clear that reference is being made to an Rh antigen. The two sets of symbols which have been proposed are shown in Table I.

TABLE I—NAMES OF RH-HR ANTIGENS

Original names	*Fisher-Race symbols*
Rh′ and Hr′	Rh C and Rh c
Rh_0 and Hr_0	Rh D and Rh d
Rh″ and Hr″	Rh E and Rh e

As is indicated in Table I the 6 antigens exist in pairs. A member of a given pair may occur without the other member in the blood of a given individual, or in combination with the other one. Hence with respect to each pair, 3 blood types are possible. Each of the 3 possible blood types relative to a given pair may exist in combination with each of the 3 possible types of each of the 2 other pairs. Accordingly 27 Rh-Hr blood types are possible. These 27 types may be designated by the original names, by the letters of Fisher and Race or by a set of abbreviated symbols advocated by Wiener. As I have already indicated, I personally prefer the CDE system but with the symbol Rh appearing before the blood type if it is not immediately clear that reference is being made to an Rh type. The original names are cumbersome and the abbreviated names of Wiener are not descriptive. The latter may be perfectly acceptable as abbreviations in a particular laboratory but in my opinon they are not the most acceptable for general use. The CDE system corresponds closely to the A-B or M-N terminology in indicating exactly the antigen present in the blood.

Landsteiner and Wiener were the first to report on the inheritance of the Rh blood factor. This was in 1941 when only 1 antigen was known, namely the one now called Rh_0 or D. These two investigators

TABLE II—THE 27 RH-HR BLOOD TYPES

Blood type using the original names of the antigens	*Recommended names*
1. Rh′ Rh_0 Rh″	Rh CDE
2. Rh′ Rh_0 Rh″Hr″	Rh CDEe
3. Rh′ Rh_0 Hr″	Rh CDe
4. Rh′ Rh_0 Hr_0Rh″	Rh CDdE
5. Rh′ Rh_0 Hr_0 Rh″ Hr″	Rh CDdEe
6. Rh′ Rh_0 Hr_0 Hr″	Rh CDde
7. Rh′ Hr_0 Rh″	Rh CdE
8. Rh′ Hr_0 Rh″ Hr″	Rh CdEe
9. Rh′ Hr_0 Hr″	Rh Cde
10. Rh′ Hr′ Rh_0 Rh″	Rh CcDE
11. Rh′ Hr′ Rh_0 Rh″ Hr″	Rh CcDEe
12. Rh′ Hr′ Rh_0 Hr″	Rh CcDe
13. Rh′ Hr′ Rh_0 Hr_0 Rh″	Rh CcDdE
14. Rh′ Hr′ Rh_0 Hr_0 Rh″ Hr″	Rh CcDdEe
15. Rh′ Hr′ Rh_0 Hr_0 Hr″	Rh CcDde
16. Rh′ Hr′ Hr_0 Rh″	Rh CcdE
17. Rh′ Hr′ Hr_0 Rh″ Hr″	Rh CcdEe
18. Rh′ Hr′ Hr_0 Hr″	Rh Ccde
19. Hr′ Rh_0 Rh″	Rh cDE
20. Hr′ Rh_0 Rh″ Hr″	Rh cDEe
21. Hr′ Rh_0 Hr″	Rh cDe
22. Hr′ Rh_0 Hr_0 Rh″	Rh cDdE
23. Hr′ Rh_0 Hr_0 Rh″ Hr″	Rh cDdEe
24. Hr′ Rh_0 Hr_0 Hr″	Rh cDde
25. Hr′ Hr_0 Rh″	Rh cdE
26. Hr′ Hr_0 Rh″ Hr″	Rh cdEe
27. Hr′ Hr_0 Hr″	Rh cde

postulated that a dominant autosomal gene existed which was responsible for the then known antigen. As this hypothesis was originally presented an individual who was Rh positive (Rh+) was either homozygous dominant, Rh Rh, or heterozygous, Rh rh; whereas an individual who was Rh negative (Rh—) was homozygous recessive, rh rh. The genetic results expected according to this original hypothesis are shown in Table III.

When Levine discovered the first Hr antigen, now called Hr′ or c, it became apparent that the original hypothesis of a dominant and a recessive allele could no longer be defended, at least, not in its entirety, because the so-called recessive gene

TABLE III—LANDSTEINER-WIENER GENETIC HYPOTHESIS (1941)

Genes	*Genotypes*	*Phenotypes*
Rh	Rh Rh	Rh positive (Rh+)
rh	Rh rh	
	rh rh	Rh negative (Rh—)

Possible matings	*Phenotypic ratio expected*
1. Rh Rh x Rh Rh	1 Rh+
2. Rh Rh x Rh rh	1 Rh+
3. Rh Rh x rh rh	1 Rh+
4. Rh rh x Rh rh	¾ Rh+ : ¼ Rh—
5. Rh rh x rh rh	½ Rh+ : ½ Rh—
6. rh rh x rh rh	1 Rh—

was found to produce an antigen and found to be as dominant as its allele. In other words, no dominance or equal dominance was found to exist. The results relative to the inheritance of Rh′ and Hr′ might then have been presented as shown in Table IV.

TABLE IV—GENETIC HYPOTHESIS FOLLOWING DISCOVERY OF Hr′ (Rh c) BY LEVINE

Genes	*Genotypes*	*Phenotypes*
Rh^C	Rh^C Rh^C	Rh C
Rh^c	Rh^C Rh^c	Rh Cc
	Rh^c Rh^c	Rh c

Possible matings	*Phenotypic ratio expected*
1. Rh^CRh^C x Rh^CRh^C	1 Rh C
2. Rh^CRh^C x Rh^CRh^c	½ Rh C : ½ Rh Cc
3. Rh^CRh^C x Rh^cRh^c	1 Rh Cc
4. Rh^CRh^c x Rh^CRh^c	¼ Rh C : 2/4 Rh Cc : ¼ Rh c
5. Rh^CRh^c x Rh^cRh^c	½ Rh Cc : ½ Rh c
6. Rh^cRh^c x Rh^cRh^c	1 Rh c

In Table IV the two alleles are designated by the basic locus symbol Rh and distinguished by the superscripts C and c. This is in accordance with a proposal which will be presented later for the symbols of all Rh genes. It should be noted especially that the phenotypic ratios shown in Table IV differ in certain instances from those shown in Table III.

As the second, third and fourth antigens were reported by various investigators and shown to have a hereditary basis, Wiener postulated that the genes responsible for all of these variations occupied a single locus, in other words, that a series of multiple alleles existed. He now assumes at least 8 alleles.

In 1944 Fisher and Race proposed a 3 linked-loci hypothesis with crossing over occurring or having occurred between the 3 loci. According to this hypothesis 8 homologous chromosomes, each with a different gene combination, may exist in a population. Fisher and Race have given the 3 pairs of genes the same names as the corresponding antigens, namely, C and c, D and d, and E and e. In my opinion this usage is an unfortunate one. If the 3 locus hypothesis should prove to be the correct one it would be preferable to use Rh as the basic locus symbol for all three loci and the letters CDE as superscripts. One specific objection to the use of C as a locus symbol is that it has previously been used in mammalian genetics, including human, for a locus affecting skin pigmentation or skin color. The 8 possible gene combinations on chromosomes, which are postulated by the 3 locus hypothesis, are shown in Table V.

As additional antigens were discovered and shown to be inherited, Wiener proposed symbols for the additional alleles which he assumed to exist. These symbols he has changed from time to time but his most recent set is probably that shown in Table V. In the opinion of many investigators, even those who favor the 8 allele hypothesis, these gene symbols proposed and strongly defended by Wiener are not fortunate choices. Among the arguments advanced against them is that they are not descriptive or suggestive of the actions which the alleles produce. Furthermore, they are not

TABLE V—GENE SYMBOLS

8 allele hypothesis		3 locus hypothesis		
Gene symbols of 8 alleles		*8 Gene combinations on chromosomes*		
Wiener	*Strandskov*			
R^z	Rh^{CDE}	Rh^C	Rh^D	Rh^E
R^1	Rh^{CDe}	Rh^C	Rh^D	Rh^e
r^y	Rh^{CdE}	Rh^C	Rh^d	Rh^E
r'	Rh^{Cde}	Rh^C	Rh^d	Rh^e
R^2	Rh^{cDE}	Rh^c	Rh^D	Rh^E
R^o	Rh^{cDe}	Rh^c	Rh^D	Rh^e
r''	Rh^{cdE}	Rh^c	Rh^d	Rh^E
r	Rh^{cde}	Rh^c	Rh^d	Rh^e

easily presented in long hand or in print without error. For example, the prime superscript and number 1 superscript are easily mistaken. Finally the use of some capital letters and some lower case letters is not in accordance with accepted genetic rules when no dominance or equal dominance of the alleles exists. Because of the numerous objections to Wiener's symbols which have been advanced I have proposed the use of Rh as the basic locus symbol and C D E letters as superscripts. In the proposed system the superscripts indicate specifically the antigens produced by each gene, if the 8 allele hypothesis is the correct one. Nearly the only valid argument in favor of Wiener's symbols is that they have priority. This argument deserves considerable consideration but we must also remember that whatever system is adopted now will be used for all time to come. Hence any one system should not be adopted lightly.

According to the 8 allele hypothesis 36 genotypes are possible. However, only 27 phenotypes or blood types should be produced, because some of the genotypes give duplicate phenotypes. The 36 genotypes and 27 phenotypes using both Wiener's symbols and those proposed by me are presented in Table VI. Only 27 genotypes are possible according to the 3 locus hypothesis. These are not shown in Table VI because they may be read directly from the 27 phenotypes which are indicated by the use of the CDE system of letters.

Since two hypotheses have been proposed to account for the inheritance of Rh-Hr blood types, and neither one is universally accepted, attempts have been made to determine which one is the correct one. To do so is not easy, but several types of discriminating evidence are possible. I shall mention and discuss briefly three of these possible lines, namely: 1) serological evidence, 2) cross-over results, and 3) gene, genotypic and phenotypic frequency analyses.

The possibly discriminating serological evidence is of the following type. According to the 8 allele hypothesis each gene is capable of producing 3 different antigens, whereas according to the 3 locus hypothesis each gene is responsible only for a single antigen. If we examine the action of other human genes which are known to be responsible for the production of antigens we find that each gene is responsible for the production of only 1 antigen. This at least is true of the genes responsible for A-B and M-N antigens. This is the simplest relationship imaginable and, therefore, seemingly the most probable. It does not follow, however, that the other relationship is impossible, namely, that a single gene can effect the production of 3 separate antigens as the 8 allele hypothesis assumes. Thus it will be apparent that it is my opinion that the serological evidence favors the 3 locus hypothesis but not to the extent of ruling out the 8 locus hypothesis.

The possible genetic evidence which may discriminate between the two proposed hypotheses is, as I have already stated, of two major types, namely 1) cross-over evidence, and 2) evidence obtained from an analysis of gene, genotypic and phenotypic frequencies in populations.

Cross-over evidence should be obtainable from a study of mating results if the 3 locus hypothesis is the correct one. By cross-over results is meant evidence that genes have been exchanged between homologous chromosomes in meiosis. To illustrate the results expected if crossing over occurs, let us assume a female of blood type Rh CcDdEe and who received the gene or genes responsible for the antigens C, D and

TABLE VI—GENOTYPES AND PHENOTYPES EXPECTED ACCORDING TO 8 ALLELE HYPOTHESIS

Proposed symbols (Strandskov)		*Wiener symbols*	
Genotypes	*Phenotypes*	*Genotypes*	*Phenotypes*
1. Rh^{CDE} Rh^{CDE}	1. Rh CDE	1. R^zR^z	1. R_zR_z
2. Rh^{CDE} Rh^{CDe}	2. Rh CDEe	2. R^zR^1	2. R_zR_1
3. Rh^{CDe} Rh^{CDe}	3. Rh CDe	3. R^1R^1	3. R_1R_1
4. Rh^{CDE} Rh^{CdE}	4. Rh CDdE	4. R^zr^y	4. R_zr_y
5. Rh^{CDE} Rh^{Cde} or Rh^{CdE} Rh^{CDe}	5. Rh CDdEe	5. R^zr' or r^yR^1	5. R_zr'
6. Rh^{CDe} Rh^{Cde}	6. Rh CDde	6. R^1r'	6. R_1r'
7. Rh^{CdE} Rh^{CdE}	7. Rh CdE	7. r^yr^y	7. r_yr_y
8. Rh^{CdE} Rh^{Cde}	8. Rh CdEe	8. r^yr'	8. r_yr'
9. Rh^{Cde} Rh^{Cde}	9. Rh Cde	9. $r'r'$	9. $r'r'$
10. Rh^{CDE} Rh^{cDE}	10. Rh CcDE	10. R^zR^2	10. R_zR_2
11. Rh^{CDE} Rh^{cDe} or Rh^{CDe} Rh^{cDE}	11. Rh CcDEe	11. R^zR^o or R^1R^2	11. R_zR_0
12. Rh^{CDe} Rh^{cDe}	12. Rh CcDe	12. R^1R^o	12. R_1R_0
13. Rh^{CDE} Rh^{cdE} or Rh^{CdE} Rh^{cDE}	13. Rh CcDdE	13. R^zr'' or r^yR^2	13. R_zr''
14. Rh^{CDE} Rh^{cde} or Rh^{CDe} Rh^{cdE} or Rh^{CdE} Rh^{cDe} or Rh^{cDE} Rh^{Cde}	14. Rh CcDdEe	14. R^zr or R^1r'' or r^yR^o or R^2r'	14. Rr_zr
15. Rh^{CDe} Rh^{cde} or Rh^{cDe} Rh^{Cde}	15. Rh CcDde	15. R^1r or R^or'	15. R_1r
16. Rh^{CdE} Rh^{cdE}	16. Rh CcdE	16. r^yr''	16. r_yr''
17. Rh^{CdE} Rh^{cde} or Rh^{Cde} Rh^{cdE}	17. Rh CcdEe	17. r^yr or $r'r''$	17. r_yr
18. Rh^{Cde} Rh^{cde}	18. Rh Ccde	18. $r'r$	18. $r'r$
19. Rh^{cDE} Rh^{cDE}	19. Rh cDE	19. R^2R^2	19. R_2R_2
20. Rh^{cDE} Rh^{cDe}	20. Rh cDEe	20. R^2R^o	20. R_2R_0
21. Rh^{cDe} Rh^{cDe}	21. Rh cDe	21. R^oR^o	21. R_0R_0
22. Rh^{cDE} Rh^{cdE}	22. Rh cDdE	22. R^2r''	22. R_2r''
23. Rh^{cDE} Rh^{cde} or Rh^{cdE} Rh^{cDe}	23. Rh cDdEe	23. R^2r or $r''R^o$	23. R_2r
24. Rh^{cDe} Rh^{cde}	24. Rh cDde	24. R^or	24. R_0r
25. Rh^{cdE} Rh^{cdE}	25. Rh cdE	25. $r''r''$	25. $r''r''$
26. Rh^{cdE} Rh^{cde}	26. Rh cdEe	26. $r''r$	26. $r''r$
27. Rh^{cde} Rh^{cde}	27. Rh cde	27. rr	27. rr

E from one of her parents, and the gene or genes responsible for the antigens, c, d, and e from her other parent. Her genetic composition might then be represented as CDE/cde, without implying that either hypothesis is the correct one. Now if she should marry a man Rh cde who may be represented as cde/cde, and they should have children, then evidence of crossing over would exist if children were born with blood types Rh Ccde, Rh cDde, Rh cdEe as well as children of blood types Rh CcDdEe and Rh cde. If no crossing over occurred then only children of the two latter blood types should be born to such a set of parents.

A large number of parents and their children have been studied for evidence of crossing over but none has been found so far. Race (1948) states that he has tested

over 150 families without detecting crossing over. Wiener and others likewise have studied many families and have found no evidence of crossing over. Hence if crossing over does occur it must be relatively rare. Thus it is apparent that the family studies presented so far give negative evidence in favor of the 3 locus hypothesis and are in agreement with the 8 allele hypothesis. They, therefore, may be said to favor the latter hypothesis. Perhaps we should mention that a single child suggesting crossing-over would not be sufficient evidence for the 3 locus hypothesis. The single observed result might represent a mutation rather than a cross-over. Only if cross-overs on a fairly large scale are observed can the evidence be said to rule out the 8 allele hypothesis and establish the 3 locus hypothesis. Fisher has suggested that indirect evidence of crossing over exists from an analysis of combinations of antigens in populations but this line of evidence, at least as advanced so far, is not very convincing.

The evidence in favor of either of the two proposed hypotheses based on observed gene, genotypic and phenotypic frequencies in populations is somewhat complex and cannot be dealt with in detail here but perhaps we may outline a few of the more direct lines of reasoning. By examining fairly large numbers of individuals in several different populations Wiener has obtained evidence that observed phenotypic frequencies agree fairly closely with frequencies expected on the basis of the 8 allele hypothesis. The British workers have been interested in comparing observed gene combinations on chromosomes with expected frequencies. They do not, however, assume that crossing has occurred to the extent that the genes at the different loci have reached combination frequencies comparable to random assortment. This is usually what would be expected if crossing over had occurred at all between the 3 loci. Rife has recently tested the 3 locus hypothesis by examining phenotypic frequencies on the assumption that equilibrium gene combinations have been reached. He finds that the observed phenotypic frequencies do not agree with those expected when this assumption is made. In other words he concludes that observed phenotypic frequencies do not agree closely with those expected on the basis of a 3 locus hypothesis. It must be admitted, however, that the test as applied may not be completely valid without a consideration of the role of selection or the make up of the sample population which was tested. Nevertheless, it seems that the gene, genotypic and phenotypic frequency analyses made so far favor on the whole the 8 allele hypothesis of Wiener rather than the 3 locus hypothesis of Fisher and Race.

SUMMARY

The following statements appear permissible relative to the genetics of the Rh-Hr Blood Factors.

1. The Rh-Hr blood types are completely genetically determined, that is, there is always a complete correspondence between phenotype and genotype.

2. An individual does not have an Rh-Hr antigen in his blood which is not present in at least one of his parents.

3. Neither of the two genetic hypotheses proposed to account for the inheritance of the Rh-Hr blood types has been completely established at the present time. The majority of the evidence, however, appears to favor the 8 allele hypothesis of Wiener rather than the 3 locus hypothesis of Fisher and Race.

4. Despite the fact that neither genetic hypothesis has been established, Rh-Hr blood tests may be used as evidence in legal cases of disputed paternity or baby mix up. However, evidence based on mode of inheritance must not be used.

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Medicolegal Aspects of the Rh-Hr Blood Types

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It was originally intended to confine this paper to the medicolegal applications of the Rh-Hr types, but I find that in order to make the subject intelligible it is necessary first to review the serology and genetics of the A-B-O blood groups and the M-N types. While it is true that the Rh-Hr types are more complicated than the A-B-O groups or the M-N types, the principles involved are the same, and knowledge of the facts and of the problems relating to the A-B-O and M-N types facilitates mastering the Rh-Hr blood types. Also the supposed simplicity of the A-B-O groups and the M-N types has been overemphasized, because when *all* the facts known concerning these two systems are taken into account the situation is no longer simple. In view of the clinical importance of the Rh-Hr types, the physician is constantly confronted with all the intricacies of this system while he is not compelled to learn the more refined facts concerning the other systems. The serologist and the medicolegal expert, however, must know the facts in their entirety.

TABLE I—THE FOUR LANDSTEINER BLOOD GROUPS

Blood groups (Phenotypes)	*Reactions of blood cells with serums*	
	Anti-A	*Anti-B*
O	—	—
A	+	—
B	—	+
AB	+	+

In Table I we have summarized the reactions given by human red blood cells when tested with anti-A serum and anti-B serum, determining the four Landsteiner blood groups. This represents about all that the average physician is required to know concerning this subject, which accounts for its apparent simplicity. As will be pointed out shortly, however, the situation is actually far more complicated. At this point, it should be emphasized that for medicolegal